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(54) **Drug delivery system.**

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Description

This invention relates to a method for the manufacture of adsorbates for use in drug delivery systems and to the adsorbates and drug formulations thereby obtained.

It is frequently desirable to delay the release of an active substance from a pharmaceutical formulation in vivo. For example, it may be desirable to delay release of the active substance within the body so that the active substance is released at a particular target site. Various coated tablets are available which are resistant to gastric juices but which are readily soluble in the higher pH environment of the small intestine. Various controlled absorption pharmaceutical formulations are also available which have a particular dissolution pattern, resulting in a controlled absorption of the active substance and, therefore, more effective medication. For example, controlled absorption pellets of the latter type for oral administration are described in the Applicants' EP-A-0 122 077, EP-A-0 123 470, EP-A-0 156 077, EP-A-0 149 920 and European Patent Application No. 86 308 810.0.

The use of many active substances in therapy is complicated by solubility problems. In the case of some insoluble drugs like nifedipine co-precipitates thereof with certain polymers are known, said co-precipitates having been formed into tablets by conventional tabletting procedures. Such co-precipitates however normally require a polymer to active drug ratio exceeding 3:1 in order to be effective in producing products characterised by high bioavailability with prompt peak blood levels.

Pharmaceutical formulations based on an adsorbate of a drug within a cross-linked polymer, such as cross-povidone, are also known. Furthermore, solid, rapidly absorbable medicament formulations comprising a dihydropyridine, polyvinylpyrrolidone with an average molecular weight of 15,000 to 50,000 and cross-linked insoluble polyvinylpyrrolidone are known from EP-A-0167909.

EP-A-123668 discloses a rapidly absorbable medicament formulation comprising glafenine as active ingredient. The formulation also comprises a solid acid, a binder and a disintegrant. The formulation is coated to resist dissolution in the mouth which would give an unpleasant taste.

It is an object of the present invention to provide an improved drug delivery system wherein the bioavailability of an otherwise poorly bioavailable active substance is enhanced and effective controlled release formulations thereof can be produced.

Accordingly, the invention provides a sustained release drug delivery matrix system comprising:

(i) an adsorbate of a mixture of 1 part by weight of a pharmaceutically useful active ingredient and from 0.1 to 10 parts by weight of an inactive substance adsorbed on a cross-linked polymer in a ratio of 1 part by weight of said mixture to 0.5 to 20 parts by weight of cross-linked polymer, said inactive substance being selected to modify the dissolution of the active drug from the cross-linked polymer in vivo; and

(ii) a polymer or mixture of polymers;

said matrix system being formed by granulating said adsorbate and blending same with a polymer or mixture of polymers, the amount of said polymer or polymers being effective to produce the desired sustained release effect.

The existence of the drug (active ingredient) in the pore spaces of the cross-linked polymer can be confirmed by x-ray diffraction studies. In the case of certain water-insoluble drugs, the formation of the adsorbate results in an amorphous state which can be verified by x-ray diffraction and, in addition, differential scanning calorimetery.

The inactive substance is preferably present in the adsorbate in an amount of 0.5 - 3 parts by weight relative to I part by weight of the active ingredient. Furthermore, the formulation preferably contains I part by weight of said mixture relative to 1-10 parts by weight of cross-linked polymer.

The invention also provides a process for preparing a sustained release drug delivery matrix system as defined above, which comprises dissolving the active ingredient and the inactive substance in a common solvent, mixing the solution thereby obtained with a given quantity of the cross-linked polymer so as to permit adsorption of said active ingredient and said inactive substance to said cross-linked polymer and removing the solvent, granulating the product thereby obtained and blending it with a polymer or mixture of polymers, the amount of said polymers being effective to produce the desired sustained release effect.

The solvent used is any pharmaceutically suitable co-solvent for the active drug and the inactive substance.

The solvent is suitably selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof.

Especially preferred solvents include water, hexane, heptane, methanol, ethanol, isopropyl alcohol, acetone, methylethyl ketone, methylisobutyl ketone, methylene chloride, chloroform, carbon tetrachloride, toluene, xylene and tetrahydrofuran.

The inactive substance is chosen to modify the dissolution of the active drug from the cross-linked polymer such that a water soluble inactive substance will serve to enhance the rate of active drug leaching from the cross-linked polymer. Conversely, a water insoluble material would serve to impede the rate of active ingredient leaching from the cross-linked polymer.

The inactive substance is also chosen to modify the crystalline properties of the active ingredient both in the sustained release drug delivery matrix system as prepared and in vivo after administration of the system.

An especially preferred cross-linked polymer is cross-povidone (Polplasdone XL (GAF), Kollidon CL (BASF) Polplasdone XL and Kollidon CL are Trade Marks). Others include cross-linked carboxymethylcellulose and cross-linked methylcellulose.

Any drug, subject to the above proviso, is suitable for use as active ingredient in the system according to the present invention. However, preferred drugs include ibuprofen, acylovir, 5-amino-salicyclic acid, dextromethorphan, propranolol, theophylline, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxicam, diclofenac, indomethacin, amoxycillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, lincomycin, co-dergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, nicardipine, 4-(2, 1, 3-bensoxadiasol-4-yl)-2, 6-dimethyl-1, 4-dihydro-3-isopropyloxycarbonyl-pyridine-5-carboxylic acid methyl ester, atenolol, lorazempam, glibenclamide, salbutamol, spironolactone, chlorpheniramine maleate, carboxamine maleate, potassium chloride and metoprolol tartrate.

Especially preferred active ingredients include diclofenac, theophylline, felodipine, nifedipine, nicardipine, nitrendipine, 4-(2, 1, 3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydro-3-isopropyloxycarbonyl-pyridine-5-carboxylic acid methyl ester, co-dergocrine mesylate, oxendolone, azidothymidine (AZT), spironolactone and chlorpheniramine maleate.

The choice of inactive substance for use in controlling the dissolution of the adsorbed active drug according to the present invention is determined by the particular pharmacological properties desired. For example, a water insoluble inactive substance may be used to delay the release of a highly water soluble drug.

Examples of inactive substances include inert polymers such as, for example, polyvinyl alcohol, polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, alkyl-celluloses such as methyl- and ethylcellulose, shellac, polymers sold under the trademark Eudragit, polyethylene glycol, sodium alginate, galactomannone or carboxypolymethylene or mixtures thereof.

Eudragit polymers are polymeric lacquer substances based on acrylates and/or methacrylates.

Especially suitable Eudragits for use as inactive substances in the system according to the invention include co-polymers of acrylic and methacrylic acid esters of varying permeability to the active ingredient and aqueous media.

Other suitable inactive substances for use in the system according to the invention include sugars and many organic acids, such as adipic acid, ascorbic acid, citric acid, fumaric acid, maleic acid, succinic acid or tartaric acid.

The choice of inactive substance is generally made by reference to the solubility of the active substance and will usually have its own solubility inversely proportional to that of the active drug. Therefore, water insoluble, polymeric materials have use in conjunction with highly water-soluble active drugs.

In the sustained release drug delivery matrix system according to the invention as defined above the adsorbate is granulated and blended with a polymer or mixture of polymers which gels in the presence of water, and optionally other ingredients. The blend thereby obtained can be tabletted or encapsulated according to conventional methods, thereby yielding a long acting controlled release matrix system which also exhibits improved drug absorption. Suitable polymers for blending with the adsorbate for subsequent tabletting or encapsulation are any one of the inert polymers cited above, which include both water soluble and water insoluble polymers. An especially suitable group of polymers is the polymers sold under the Trade Mark Methocel. If one wishes to delay release of the active ingredient in vivo in capsule or tablet form a combination of a water soluble and a water insoluble polymer or a mixture of such polymers will be used, with the ratio of the water soluble to water insoluble polymer being varied to give the desired rate of release. Similarly, in the case of polymers/copolymers of varying permeability the permeabililty characteristic of the polymers/copolymers will be chosen to give the desired rate of release.

The adsorbates used in the sustained release drug delivery matrix according to the present invention result in improved controlled drug delivery relative to known activ drug adsorbates in cross-linked polymers, since the adsorbates according to the present invention yield a matrix system exhibiting sustained release of active drug and improved absorption of said active drug in vivo.

The invention will be further illustrated with reference to the following Examples.

EXAMPLE 1

Polyvinylpyrrolidone K-30 (Trade Mark) (2 kg) was dissolved in isopropylalcohol (10 kg). Nifedipine (1 kg) was then added to this solution and allowed to dissolve. The solution thereby obtained was then adsorbed onto cross-linked carboxymethylcellulose (4 kg) and the solvent evaporated. The resulting powder was then passed through an oscillating granulator to obtain a finer particle size. X-ray diffraction and differential scanning calorimetry studies were performed on the powder and demonstrated that the nifedipine was in an amorphous form. The powder (30%) was then tabletted with the following ingredients.

Methocel K100LV (Trade Mark)	8.0%
Avicel pH101 (Trade Mark)	61.5%
Magnesium stearate	0.5%

to obtain a tablet containing 20 mg of active ingredient. An x-ray diffraction pattern of the tablet was obtained which demonstrated the amorphous nature of the nifedipine had been retained.

In the above Example, the ratio of nifedipine, polyvinylpyrrolidone and cross-linked carboxymethylcellulose may be altered within the limits which retain the amorphous nature of the drug. This also applies in the case of the subsequent Examples.

Furthermore, the Methocel used may be Methocel K4M, K15M, K100M, or E, J, F grades depending on the release characteristics desired.

The gel forming polymer may be used in an amount of 3 - 50% with proportional changes in the percentage of adsorbate used. This also applies in the case of the subsequent Examples.

EXAMPLE 2

Polyvinylpyrrolidone K-30 (Trade Mark) (2 kg) was dissolved in isopropyl alcohol (10 kg). Nicardipine (1kg) was then added to this solution and allowed to dissolve. The solution thereby obtained was then adsorbed onto a cross-linked carboxymethylcellulose (Croscarmellulose - Trade Mark) (4 kg) and the solvent evaporated. The resulting powder was passed through an oscillating granulator to obtain a finer particle size. The powder (60%) was then tabletted with the following ingredients:

Methocel K100M (Trade Mark)	8.0%
Avicel pH101 (Trade Mark)	31.5%
Magnesium stearate	0.5%

to obtain a tablet containing 60 mg of active ingredient.

EXAMPLE 3

The procedure of Example 1 was repeated except that the nifedipine was replaced by an equal amount (1 kg) of (4-(2,1,3-benzoxadiazol-4-yl)-2, 6-dimethyl-1, 4-dihydro-3-isopropyloxycarbonyl-pyridine-5-carboxylic acid methyl ester to obtain tablets containing 10 mg mg of active ingredient.

EXAMPLE 4

Spironolactone (1 kg) and polyvinylpyrrolidone K-30 (2 kg) were dissolved in a common solvent ethanol (10kg).

Cross-povidone (4 kg) was added to the solution of spironolactone and polyvinylpyrrolidone so as to permit adsorption of the spironolactone and polyvinylpyrrolidone to the cross-povidone. The solvent was then removed by heating. The ability of the spironolactone to be dissolved out of the cross-povidone is enhanced by the ready solubility of the polyvinylpyrrolidone in water. A given quantity (50%) of the adsorbate was granulated and blended with hydroxypropylmethylcellulose (50%). The blend thereby obtained was filled into soft gelatine capsules so as to obtain capsules containing 50 mg of spironolactone.

EXAMPLE 5

Anhydrous theophylline (0.5 kg) and citric acid (1 kg) were dissolved in isopropyl alcohol (10 kg) and adsorbed on cross-povidone (2 kg) in the manner described in Example 1. A given quantity (50%) of the adsorbate was granulated and blended with Eudragit RL (50%). The blend was then filled into hard gelatine capsules (422 mg) so as to obtain capsules containing 300 mg of anhydrous theophylline. The presence of the citric acid was found to enhance the solubility of the anhydrous theophylline at pH values in excess of 7 and was suitable for use in a long acting or sustained release drug formulation.

EXAMPLE 6

Chlorpheniramine maleate (0.5 kg) and ethylcellulose (1 kg) which is insoluble in water and thereby inactive in an aqueous environment were dissolved in isopropyl alcohol (10 kg) and adsorbed onto cross-povidone (2 kg) in the manner described in Example 1. The powder (30%) was then tabletted with the following ingredients:

Methocel K15M (Trade Mark)	8.0%
Avicel pH101 (Trade Mark)	61.5%
Magnesium stearate	0.5%

to obtain a tablet containing 10 mg of chlorpheniramine maleate.

EXAMPLE 7

Polyvinylpyrrolidone (K-30) (0.75 kg) was dissolved in methylene chloride (12 kg). Nifedipine (1 kg) was then added to this solution and allowed to dissolve. The solution thereby obtained was then adsorbed onto cross-linked carboxymethylcellulose (3 kg) and the solvent evaporated. The resulting powder was then passed through an oscillating granulator to obtain a fine particle size. X-ray diffraction and differential scanning calorimetry studies showed that the drug was in amorphous form in this adsorbate. The powder (30%) was then tabletted with the following ingredients:

Methocel K100 LV (Trade Mark)	10%
Avicel pH101 (Trade Mark)	59.5%
Magnesium stearate	0.5%

to obtain a tablet containing 20 mg active ingredient.

Similar x-ray diffraction and differential scanning calorimetry studies showed this product to be amorphous.

EXAMPLE 8

The procedure employed was similar to that in Example 7 except that the amount of polyvinylpyrrolidone (K-30) used was 0.5 kg and also included was polyethylene glycol 6000 (1 kg).

EXAMPLE 9

The procedure employed was similar to that in Example 8 except that the polyethylene glycol was replaced by methylcellulose (0.75 kg).

EXAMPLE 10

The procedure employed was similar to that in Example 7 except that methylcellulose (0.75 kg) was used instead of polyvinylpyrrolidone (0.75 kg).

EXAMPLE 11

The procedure employed was similar to that in Example 8 except that polyvinylpyrrolidone (0.5 kg) was replaced by methylcellulose (0.5 kg).

EXAMPLE 12

The procedure used was similar to that employed in Example 7 except the polyvinylpyrrolidone (0.75 kg) was replaced by polyethylene glycol 6000 (1.5 kg).

EXAMPLE 13

Polyvinylpyrrolidone K-25 (Trade Mark) (0.50 kg) was dissolved in isopropyl alcohol (10 kg). Diclofenac (1kg) was added to this solution and allowed to dissolve. The solution thereby obtained was then adsorbed onto cross-linked polyvinylpyrrolidone (2.5 kg) and the solvent evaporated. The resulting powder (60%) was treated in Example 1 and tabletted with the following ingredients:

Methocel K100LV (Trade Mark)	16.5%
Avicel pH101 (Trade Mark)	23.0%
Calcium stearate	0.5%

to obtain a tablet containing 100 mg active ingredient.

EXAMPLE 14

Methocel A4M (Trade Mark) (0.15 kg) was dissolved in dichloromethane (10 kg). Oxendolone (1 kg) was added to the solution and dissolved. The resulting solution was adsorbed onto cross-povidone (4 kg) and treated as per Example 1.

The resulting powder (80%) was tabletted with the following ingredients:

Methocel K100LV (Trade Mark)	1.5%
Avicel pH101 (Trade Mark)	13.0%
Magnesium stearate	0.5%

to obtain a tablet containing 100 mg active ingredient.

EXAMPLE 15

Example 1 was repeated except the nifedipine formulation (50%) was tabletted with the following ingredients.

Sodium alginate	15.0%
Pregelatinized starch N.F.	33.5%
Talc	1.5%

EXAMPLE 16

Example 2 was repeated except the nicardipine formulation (50%) was tabletted with the following ingredients:

Lactose U.S.P.	10.0%
Eudragit R.S.	10.0%
Eudragit R.L.	29.25%
Calcium stearate	0.75%

EXAMPLE 17

Example 6 was repeated except the chlorpheniramine maleate formulation (40%) was tabletted with the following ingredients.

Dibasic calcium phosphate dihydrate N.F.	15.0%
Ethylcellulose 100 cps	15.0%
Polyethyleneglycol 6000	5.0%
Hydroxyethylcellulose	29.0%
Calcium stearate	1.0%

Claims

Claims for the following Contracting States : BE, CH, LI, DE, FR, GB, IT, NL, SE

1. A sustained release drug delivery matrix system comprising:
   (i) an adsorbate of a mixture of 1 part by weight of a pharmaceutically useful active ingredient and from 0.1 to 10 parts by weight of an inactive substance adsorbed on a cross-linked polymer in a ratio of 1 part by weight of said mixture to 0.5 to 20 parts by weight of cross-linked polymer, said inactive substance being selected to modify the dissolution of the active drug from the cross-linked polymer in vivo; and
   (ii) a polymer or mixture of polymers;
   said matrix system being formed by granulating said adsorbate and blending same with a polymer or mixture of polymers, the amount of said polymer or polymers being effective to produce the desired sustained release effect.

2. A sustained release drug delivery matrix system according to claim 1, characterised in that the polymer or mixture of polymers, with which the adsorbate is blended, gels in the presence of water.

3. A sustained release drug delivery system according to claim 2, characterised in that the polymer which gels in the presence of water is selected from polyvinyl alcohol, polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, alkylcelluloses, copolymers of acrylic and methacrylic acid esters, polyethylene glycol, sodium alginate, galactomannone or carboxypolymethylene or a mixture thereof.

4. A sustained release drug delivery matrix system according to claim 3, characterised in that the polymer which gels in the presence of water is selected from methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, or a copolymer of acrylic and methacrylic acid esters, or a mixture thereof.

5. A sustained release drug delivery matrix system according to any one of claims 2 to 4, characterised in that said gel forming polymer is present in an effective amount between 3 to 50% by weight of the system.

6. A sustained release drug delivery matrix system according to any one of claims 1 to 5, characterised in that the active ingredient is a dihydropyridine, the inactive substance is a polyvinylpyrrolidone, polyethyleneglycol or methylcellulose or a mixture thereof, and the cross-linked polymer is a cross-linked polyvinylpyrrolidone, carboxymethylcellulos or methylcellulose.

7. A sustained release drug delivery matrix system according to any one of claims 1 to 6, characterised in that the inactive substance is present in an amount of 0.5 to 3 parts by weight relative to one part by weight of the active ingredient.

8. A sustained release drug delivery matrix system according to any one of claims 1 to 7, characterised in that it contains 1 part by weight of said mixture relative to 1 to 10 parts by weight of cross-linked polymer.

9. A process for preparing a sustained release drug delivery matrix system according to any one of claims 1 to 8, characterised in that said process comprises dissolving the active ingredient and the inactive substance in a common solvent, mixing the solution thereby obtained with a given quantity of the cross-linked polymer so as to permit adsorption of said active ingredient and said inactive substance to said cross-linked polymer and removing the solvent, granulating the product thereby obtained and blending it with a polymer or mixture of polymers, the amount of said polymers being effective to produce the desired sustained release effect.

10. A process according to claim 9, characterised in that the solvent used is any pharmaceutically suitable co-solvent for the active ingredient and the inactive substance.

11. A process according to claim 9 or 10, characterised in that the solvent is selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof.

Claims for the following Contracting State : ES

1. A process for preparing a sustained release drug delivery matrix system comprising granulating an adsorbate of a mixture of 1 part by weight of a pharmaceutically useful active ingredient and from 0.1 to 10 parts by weight of an inactive substance adsorbed on a cross-linked polymer in a ratio of 1 part by weight of said mixture to 0.5 to 20 parts by weight of cross-linked polymer, said inactive substance being selected to modify the dissolution of the active drug from the cross-linked polymer in vivo, and blending the granulated adsorbate with a polymer or mixture of polymers, the amount of said polymer or polymers being effective to produce the desired sustained release effect.

2. A process according to claim 1, characterised in that the polymer or mixture of polymers, with which the adsorbate is blended, gels in the presence of water.

3. A process according to claim 2, characterised in that the polymer which gels in the presence of water is selected from polyvinyl alcohol, polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, alkylcelluloses, copolymers of acrylic and methacrylic acid esters, polyethylene glycol, sodium alginate, galactomannone or carboxypolymethylene or a mixture thereof.

4. A process according to claim 3, characterised in that the polymer which gels in the presence of water is selected from methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, or a copolymer of acrylic and methacrylic acid esters, or a mixture thereof.

5. A process according to any one of claims 2 to 4, characterised in that said gel forming polymer is present in an effective amount between 3 to 50% by weight of the system.

6. A process according to any one of claims 1 to 5, characterised in that the active ingredient is a dihydropyridine, the inactive substance is a polyvinylpyrrolidone, polyethyleneglycol or methylcellulose or a mixture thereof, and the cross-linked polymer is a cross-linked polyvinylpyrrolidone, carboxymethylcellulose or methylcellulose.

7. A process according to any one of claims 1 to 6, characterised in that the inactive substance is present in the adsorbate in an amount of 0.5 to 3 parts by weight relative to one part by weight of the active ingredient.

8. A process according to any one of claims 1 to 7, characterised in that the adsorbate contains 1 part by weight of said mixture relative to 1 to 10 parts by weight of cross-linked polymer.

9. A process according to any one of claims 1 to 8, characterised in that said adsorbate is formed by dissolving the active ingredient and the inactive substance in a common solvent, mixing the solution thereby obtained with a given quantity of the cross-linked polymer so as to permit adsorption of said active ingredient and said inactive substance to said cross-linked polymer and removing the solvent.

10. A process according to claim 9, characterised in that the solvent used is any pharmaceutically suitable co-solvent for the active ingredient and the inactive substance.

11. A process according to claim 9 or 10, characterised in that the solvent is selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture therof.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : BE, CH, LI, DE, FR, GB, IT, NL, SE

1. Matrixsystem mit verzögerter Arzneimittelfreisetzung, welches umfaßt:
   (i) ein Adsorbat aus einen Gemisch von 1 Gewichtsteil eines pharmazeutisch geeigneten aktiven Bestandteils und 0,1 bis 10 Gewichtsteile einer inaktiven Substanz, die auf einem vernetzten Polymeren in einem Verhältnis von 1 Gewichtsteil des genannten Gemisches zu 0,5 bis 20 Gewichtsteilen des vernetzten Polymeren adsorbiert ist, wobei die genannte inaktive Substanz ausgewählt ist, um die Lösung des aktiven Arzneimittels aus dem vernetzten Polymeren in vivo zu modifizieren; und
   (ii) ein Polymer oder ein Gemisch von Polymeren,
   wobei das genannte Matrixsystem durch Granulieren des genannten Adsorbats und Vermischen desselben mit einem Polymeren oder einem Gemisch von Polymeren gebildet wird, wobei die Menge des genannten Polymeren oder der Polymere wirksam ist, um den gewünschten verzögerten Freisetzungseffekt hervorzurufen.

2. Matrixsystem mit verzögerter Arzneimittelfreisetzung nach Anspruch 1, dadurch gekennzeichnet, daß das Polymere oder das Gemisch der Polymeren, mit dem das Adsorbat vermischt ist, in Gegenwart von Wasser geliert.

3. Arzneimittelfreisetzungssystem mit verzögerter Arzneimittelfreisetzung nach Anspruch 2, dadurch gekennzeichnet, daß das Polymere, das in Gegenwart von Wasser geliert, ausgewählt ist aus Polyvinylalkohol, Polyvinylpyrrolidon, Hydroxyethylcellulose, Hydroxypropylcellulose, Hydroxypropylmethylcellulose, Natriumcarboxymethyl-cellulose, Alkylcellulosen, aus Copolymeren von Acrylsäure- und Methacrylsäureestern, Polyethylenglycol, Natriumalginat, Galactomannon oder Carboxypolymethylen oder aus einein Gemisch davon.

4. Matrixsystem mit verzögerter Arzneimittelfreisetzung nach Anspruch 3, dadurch gekennzeichnet, daß das Polymere, das in Gegenwart von Wasser geliert, ausgewählt ist aus Methylcellulose, Ethylcellulose, Hydroxypropylcellulose, Hydroxypropylmethylcellulose oder aus einein Copolymeren von Acrylsäure- und Methacrylsäureestern oder aus einem Gemisch davon.

5. Matrixsystem mit verzögerter Arzneimittelfreisetzung nach einem der Ansprüche 2 bis 4, dadurch gekennzeichnet, daß das genannte gelbildende Polymere in einer wirksamen Menge zwischen 3 bis 50 Gew. % des Systems vorhanden ist.

6. Matrixsystem mit verzögerter Arzneimittelfreisetzung nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der aktive Bestandteil ein Dihydropyridin ist, die inaktive Substanz ein Polyvinylpyrrolidon, Polyethylenglycol oder Methylcellulose oder ein Gemisch davon ist, und das vernetzte Polymere ein vernetztes Polyvinylpyrrolidon, Carboxymethylcellulose oder Methylcellulose ist.

7. Matrixsystem mit verzögerter Arzneimittelfreisetzung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die inaktive Substanz in einer Menge von 0,5 bis 3 Gewichtsteilen relativ zu 1

Gewichtsteil des aktiven Bestandteils vorhanden ist.

8. Matrixsystem mit verzögerter Arzneimittelfreisetzung nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß es 1 Gewichtsteil des genannten Gemisches relativ zu 1 bis 10 Gewichtsteilen des vernetzten Polymeren enthält.

9. Verfahren zur Herstellung eines Matrixsystems mit verzögerter Arzneimittelfreisetzung zur verzögerten Freisetzung nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß das genannte Verfahren umfaßt, Auflösen des aktiven Bestandteils und der inaktiven Substanz in einem gemeinsamen Lösungsmittel, Vermischen der so erhaltenen Lösung mit einer gegebenen Menge des vernetzten Polymeren, so daß die Adsorption des genannten aktiven Bestandteils und der genannten inaktiven Substanz an dem genannten vernetzten Polymeren ermöglicht wird, und Entfernen des Lösungsmittels, Granulieren des so erhaltenen Produkts und sein Vermischen mit einem Polymeren oder einem Gemisch von Polymeren, wobei die Menge der genannten Polymeren wirksam ist, um die gewünschte verzögerte Freisetzungswirkung hervorzurufen.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß das verwendete Lösungsmittel ein pharmazeutisch geeignetes gemeinsames Lösungsmittel für den aktiven Bestandteil und die inaktive Substanz ist.

11. Verfahren nach Anspruch 9 oder 10, dadurch gekennzeichnet, daß das Lösungsmittel ausgewählt wird aus Wasser, Alkoholen, Ketonen, halogenierten aliphatischen Verbindungen, halogenierten aromatischen Kohlenwasserstoffverbindungen,aromatischen Kohlenwasserstoffverbindungen und cyclischen Ethern oder aus einem Gemisch davon.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung eines Matrixsystems mit verzögerter Arzneimittelfreisetzung, umfassend die Granulation eines Adsorbats aus einem Gemisch von 1 Gewichtsteil eines pharmazeutisch geeigneten aktiven Bestandteils und 0,1 bis 10 Gewichtsteile einer inaktiven Substanz, die auf einem vernetzten Polymeren in einem Verhältnis von 1 Gewichtsteil des genannten Gemisches auf 0,5 bis 20 Gewichtsteile des vernetzten Polymeren adsorbiert ist, wobei die inaktive Substanz ausgewählt wird, um die Lösung des aktiven Arzneimittels aus dem vernetzten Polymeren in vivo zu modifizieren; und Vermischen des granulierten Adsorbats mit einem Polymeren oder einem Gemisch von Polymeren, wobei die Menge des genannten Polymeren oder der Polymere wirksam ist, um den gewünschten verzögerten Freisetzungseffekt hervorzurufen.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Polymere oder das Gemisch der Polymeren, mit dem das Adsorbat vermischt ist, in Gegenwart von Wasser geliert.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Polymere, das in Gegenwart von Wasser geliert, ausgewählt wird aus Polyvinylalkohol, Polyvinylpyrrolidon, Hydroxyethylcellulose, Hydroxypropylcellulose, Hydroxypropylmethylcellulose, Natriumcarboxymethylcellulose, Alkylcellulosen, aus Copolymeren von Acrylsäure- und Methacrylsäureestern, Polyethylenglycol, Natriumalginat, Galactomannon oder Carboxypolymethylen oder aus einem Gemisch davon.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß das Polymere, das in Gegenwart von Wasser geliert, ausgewählt wird aus Methylcellulose, Ethylcellulose, Hydroxypropylcellulose, Hydroxypropylmethylcellulose oder aus einem Copolymeren von Acrylsäure- und Methacrylsäureestern oder aus einem Gemisch davon.

5. Verfahren nach einem der Ansprüche 2 bis 4, dadurch gekennzeichnet, daß das genannte gelbildende Polymere in einer wirksamen Menge zwischen 3 bis 50 Gew.-% des Systems vorhanden ist.

6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der aktive Bestandteil ein Dihydropyridin ist, die inaktive Substanz ein Polyvinylpyrrolidon, Polyethylenglycol oder Methylcellulose oder ein Gemisch davon ist, und das vernetzte Polymer ein vernetztes Polyvinylpyrrolidon, Carboxymethylcellulose oder Methylcellulose ist.

7. Verfahren nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die inaktive Substanz in einer Menge von 0,5 bis 3 Gewichtsteilen relativ zu 1 Gewichtsteil des aktiven Bestandteils in dein Adsorbat vorhanden ist.

8. Verfahren nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß es 1 Gewichtsteil des genannten Gemisches relativ zu 1 bis 10 Gewichtsteilen des vernetzten Polymeren enthält.

9. Verfahren nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß das genannte Adsorbat gebildet wird, indem der aktive Bestandteil und die inaktive Substanz in einen gemeinsamen Lösungsmittel aufgelöst werden, die so erhaltene Lösung mit einer gegebenen Menge des vernetzten Polymeren vermischt wird, so daß die Adsorption des genannten aktiven Bestandteils und der genannten inaktiven Substanz an dein genannten vernetzten Polymeren ermöglicht wird, und das Lösungsmittel entfernt wird.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß das verwendete Lösungsmittel ein pharmazeutisch geeignetes gemeinsames Lösungsmittel für den aktiven Bestandteil und die inaktive Substanz ist.

11. Verfahren nach Anspruch 9 oder 10, dadurch gekennzeichnet, daß das Lösungsmittel ausgewählt wird aus Wasser, Alkoholen, Ketonen, halogenierten aliphatischen Verbindungen, halogenierten aromatischen Kohlenwasserstoffverbindungen,aromatischen Kohlenwasserstoffverbindungen und cyclischen Ethern oder aus einein Gemisch davon.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, LI, DE, FR, GB, IT, NL, SE

1. Système de matrice pour la délivrance de médicaments à libération retardée, comprenant :
   (i) un adsorbat d'un mélange de 1 partie en poids d'un constituant pharmaceutiquement actif et de 0,1 à 10 parties en poids d'une substance inactive, adsorbée sur un polymère réticulé, dans un rapport de 1 partie en poids dudit mélange pour 0,5 à 20 parties en poids de polymère réticulé, ladite substance inactive étant choisie de façon à modifier la dissolution in vivo du médicament actif à partir du polymère réticulé ; et
   (ii) un polymère ou un mélange de polymères ;
   ledit système de matrice étant formé en granulant ledit adsorbat et en le mélangeant avec un polymère ou un mélange de polymères, la quantité dudit polymère ou mélange de polymères étant efficace pour produire l'effet de libération retardée voulue.

2. Système de matrice pour la délivrance de médicaments à libération retardée, selon la revendication 1, caractérisé en ce que le polymère ou mélange de polymères, auquel est incorporé l'adsorbat, se gélifie en présence d'eau.

3. Système de matrice pour la délivrance de médicaments à libération retardée, selon la revendication 2, caractérisé en ce que le polymère qui se gélifie en présence d'eau est choisi parmi le poly(alcool vinylique), la polyvinylpyrrolidone, l'hydroxyéthylcellulose, l'hydroxypropylcellulose, l'hydroxypropylméthylcellulose, la carboxyméthylcellulose sodique, les alkylcelluloses, des copolymères d'acrylates et de méthacrylates, le polyéthylèneglycol, l'alginate de sodium, la galactomannone ou le carboxypolyméthylène ou un de leurs mélanges.

4. Système de matrice pour la délivrance de médicaments à libération retardée, selon la revendication 3, caractérisé en ce que le polymère qui se gélifie en présence d'eau est choisi parmi la méthylcellulose, l'éthylcellulose, l'hydroxypropylcellulose, l'hydroxypropylméthylcellulose ou un copolymère d'acrylates et de méthacrylates ou un de leurs mélanges.

5. Système de matrice pour la délivrance de médicaments à libération retardée, selon l'une quelconque des revendications 2 à 4, caractérisé en ce que ledit polymère formateur de gel est présent en une quantité efficace comprise entre 3 et 50 % en poids du système.

6. Système de matrice pour la délivrance de médicaments à libération retardée, selon l'une quelconque des revendications 1 à 5, caractérisé en ce que le constituant actif est la dihydropyridine, la substance inactive est la polyvinylyrrolidone, le polyéthylèneglycol ou la méthylcellulose ou un de leurs mélanges, et le polymère réticulé est la polyvinylpyrrolidone, la carboxyméthylcellulose ou la méthylcellulose réticulée.

7. Système de matrice pour la délivrance de médicaments à libération retardée, selon l'une quelconque des revendications 1 à 6, caractérisé en ce que la substance inactive est présente en une quantité de 0,5 à 3 parties en poids pour une partie en poids du constituant actif.

8. Système de matrice pour la délivrance de médicaments à libération retardée, selon l'une quelconque des revendications 1 à 7, caractérisé en ce qu'il contient 1 partie en poids dudit mélange pour 1 à 10 parties en poids de polymère réticulé.

9. Procédé de préparation d'un système de matrice pour la délivrance de médicaments à libération retardée, selon l'une quelconque des revendications 1 à 8, caractérisé en ce que ledit procédé consiste à dissoudre le constituant actif et la substance inactive dans un solvant commun, à mélanger la solution ainsi obtenue avec une quantité donnée du polymère réticulé de façon à permettre l'adsorption dudit constituant actif et de ladite substance inactive sur ledit polymère réticulé, et à éliminer le solvant, à granuler le produit ainsi obtenu et à le mélanger avec un polymère ou mélange de polymères, la quantité desdits polymères étant efficace pour produire l'effet de libération retardée voulu.

10. Procédé selon la revendication 9, caractérisé en ce que le solvant utilisé est un cosolvant quelconque, pharmaceutiquement approprié, à la fois du constituant actif et de la substance inactive.

11. Procédé selon la revendication 9 ou 10, caractérisé en ce que le solvant est choisi parmi l'eau, les alcools, les cétones, les composés aliphatiques halogénés, les composés hydrocarbonés aromatiques halogénés, les composés hydrocarbonés aromatiques et les éthers cycliques, ou un de leurs mélanges.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un système de matrice pour la délivrance de médicaments à libération retardée, consistant à granuler un adsorbat d'un mélange de 1 partie en poids d'un constituant pharmaceutiquement actif et de 0,1 à 10 parties en poids d'une substance inactive, adsorbée sur un polymère réticulé, dans un rapport de 1 partie en poids dudit mélange pour 0,5 à 20 parties en poids de polymère réticulé, ladite substance inactive étant choisie de façon à modifier la dissolution in vivo du médicament actif à partir du polymère réticulé ; et à mélanger l'adsorbat granulé avec un polymère ou un mélange de polymères, la quantité dudit polymère ou mélange de polymères étant efficace pour produire l'effet de libération retardée voulue.

2. Procédé selon la revendication 1, caractérisé en ce que le polymère ou mélange de polymères, auquel est incorporé l'adsorbat, se gélifie en présence d'eau.

3. Procédé selon la revendication 2, caractérisé en ce que le polymère qui se gélifie en présence d'eau est choisi parmi le poly(alcool vinylique), la polyvinylpyrrolidone, l'hydroxyéthylcellulose, l'hydroxypropylcellulose, l'hydroxypropylméthylcellulose, la carboxyméthylcellulose sodique, les alkylcelluloses, des copolymères d'acrylates et de méthacrylates, le polyéthylèneglycol, l'alginate de sodium, la galactomannone ou le carboxypolyméthylène ou un de leurs mélanges.

4. Procédé selon la revendication 3, caractérisé en ce que le polymère qui se gélifie en présence d'eau est choisi parmi la méthylcellulose, l'éthylcellulose, l'hydroxypropylcellulose, l'hydroxypropylméthylcellulose ou un copolymère d'acrylates et de méthacrylates ou un de leurs mélanges.

5. Procédé selon l'une quelconque des revendications 2 à 4, caractérisé en ce que ledit polymère formateur de gel est présent en une quantité efficace comprise entre 3 et 50 % en poids du système.

6. Procédé selon l'une quelconque des revendications 1 à 5, caractérisé en ce que le constituant actif est la dihydropyridine, la substance inactive est la polyvinylpyrrolidone, le polyéthylèneglycol ou la

méthylcellulose ou un de leurs mélanges, et le polymère réticulé est la polyvinylpyrrolidone, la carboxyméthylcellulose ou la méthylcellulose réticulée.

7. Procédé selon l'une quelconque des revendications 1 à 6, caractérisé en c que la substance inactive est présente dans l'adsorbat en une quantité de 0,5 à 3 parties en poids pour une partie en poids du constituant actif.

8. Procédé selon l'une quelconque des revendications 1 à 7, caractérisé en ce que l'adsorbat contient 1 partie en poids dudit mélange pour 1 à 10 parties en poids de polymère réticulé.

9. Procédé selon l'une quelconque des revendications 1 à 8, caractérisé en ce que ledit adsorbat est formé par dissolution du constituant actif et de la substance inactive dans un solvant commun, mélange de la solution ainsi obtenue avec une quantité donnée du polymère réticulé de façon à permettre l'adsorption dudit constituant actif et de ladite substance inactive sur ledit polymère réticulé, et élimination du solvant.

10. Procédé selon la revendication 9, caractérisé en ce que le solvant utilisé est un co-solvant quelconque, pharmaceutiquement approprié, à la fois du constituant actif et de la substance inactive.

11. Procédé selon la revendisation 9 ou 10, caractérisé en ce que le solvant est choisi parmi l'eau, les alcools, les cétones, les composés aliphatiques halogénés, les composés hydrocarbonés aromatiques halogénés, les composés hydrocarbonés aromatiques et les éthers cycliques, ou un de leurs mélanges.